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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/801,164	03/07/2001	Norbert W. Bischofberger	172.2USDC2	7772

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EXAMINER
LUKTON, DAVID

ART UNIT	PAPER NUMBER
1653	7

DATE MAILED: 09/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/801,164	Applicant(s) BISCHOFBERGER ET AL.	
	Examiner David Lukton	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Pursuant to the directives of paper No. 8 (filed 7/3/02), claim 52 has been amended. Claim 52 is pending.

Applicants' arguments filed 7/3/02 have been considered and found persuasive in part.

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 52 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As indicated previously, there is no evidence that any of the claimed compounds exhibit antiviral activity. Applicants have argued that the claimed compounds are prodrugs of lamivudine. However, one cannot predict the efficacy of a prodrug based on its structure. As stated in *Ex parte Forman* (230 USPQ 546, 1986) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in

that art, predictability or unpredictability of the art, and breadth of the claims. As it happens, when one takes an established drug, and modifies its structure in an effort to obtain a prodrug, "unpredictable" results are obtained. Consider the following:

- Shabat D (*Proceedings of the National Academy of Sciences* **98** (13) 7528-33, 2001) discloses a prodrug that is not activated by endogenous enzymes. This supports the conclusion of "unpredictability" in that the instantly claimed compounds may not be activated by endogenous enzymes.

- Smal (*Biochemical Pharmacology* **49** (4) 567-74, 1995) discloses (e.g., p. 572) that 2-Leu-MTX is unsuitable as a prodrug

- Saboulard (*Molecular Pharmacology* **56** (4) 693-704, 1999) discloses (e.g., page 701, col 1) that prodrugs of AZT are not effective.

- Jaffar (*Bioorganic and Medicinal Chemistry Letters* **9** (1) 113-8, 1999) discloses (e.g., table 1) prodrugs of aspirin that are not effective.

- Miyauchi M (*Chemical and Pharmaceutical Bulletin* **38** (7) 1906-10, 1990) discloses an attempt to produce orally bioavailable prodrugs of 3-thiazoliomethyl cephalosporin (compound number 1) Lipophilicity of the resulting derivatives (8-10) was suitable for passive absorption from the intestinal tract, and chemical stability in phosphate buffer solution (pH 6.86) was moderate. However, when administered orally to mice, these derivatives were mainly transformed to a novel 3-spiro cephalosporin 11, and desired reconversion to the 3-thiazoliomethyl cephalosporin was minor. These results showed that the derivatives (8-10) tested in this study did not serve as orally active prodrugs of 3-thiazoliomethyl cephalosporin 1.

- Hadad S (*Journal of Pharmaceutical Sciences*, **81** (10) 1047-50, 1992) examined the pharmacokinetics and efficacy of five monoester prodrugs of valproic acid (VPA). Valproic acid an anti-epileptic drug. Four of the five prodrugs were ineffective in mitigating symptoms of epilepsy. In addition, a pharmacokinetic- pharmacodynamic correlation was absent in the case of B-VPA and H-VPA.

- Langer (*J. Med. Chem.* **44**, 1341-1348 2001) has examined the effects of bonding a peptide, via a linker, to daunorubicin and doxorubicin. As stated (p. 1344, col 1, paragraph 3, attaching a peptide to the amino group of daunorubicin or doxorubicin eliminated activity.

- Mamber S. W. (*Journal of Pharmacology and Experimental Therapeutics* **274** (2) 877-883, 1995) discloses prodrugs of taxol. The 2'- and 7- phosphate analogs BMY46366 and BMY46489 were ineffective as prodrugs.

- Niemi (*J. Med. Chem.* **42**, 5053, 1999) prepared compounds which were intended to be prodrugs of clodronic acid. As it happened, benzoyloxyproyl esters of clodronic acid were ineffective as prodrugs.

In accordance with the foregoing, structure/activity relationships of prodrugs are "unpredictable". Accordingly, "undue experimentation would be required to practice the claimed invention.

*

Claim 52 is rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 52 now recites the following:

"R independently is selected from the group consisting of X1, X2, ... and **N(R^{6A})**

It appears that what is intended here is for the subscript "2" to be present following (R^{6A}); i.e., the following:

R independently is selected from the group consisting of X1, X2, ... and $N(R^{6.1})_2$

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

DAVID LUKTON
PATENT EXAMINER
GROUP 1800